CLAIM STATUS

Claims 62 and 110 were cancelled. Claims 49, 52, 53, 56-60, 63-65, 73, and 103 were amended. Amendments to Claims 52, 53, 56, 57, 58, 59, 60, 63-65, 73 an 103 relate to form and/or grammar only for the purpose of increasing the clarity of these claims. Support for amendment to Claim 49 may be found throughout the specification, including paragraphs [0006], [0023], [0028], and original Claims 52 and 62.

No new matter has been added.

REMARKS

Specification

The Examiner objected to the Title of the application, as not being descriptive. Applicants amended the title to clearly indicate the invention to which the claims are directed.

The Examiner objected to the abstract of the disclosure. Applicants amended the abstract to comply with the proper content, language and format of an abstract of the disclosure.

The Examiner also identified informalities in the disclosure. More specifically, the numbering of the paragraphs was inconsistent. Applicants corrected the numbering of the paragraphs at pages 1-3 to be consistent with the numbering of paragraphs at pages 4-24 of the specification.

Next, the Examiner pointed out that the trademark names should be capitalized and accompanied by generic terminology. Applicants amended the paragraphs [0063] and [0075] of the specification to clarify the use of trademark names MYLAR® and KOLLIDONE® and provided the appropriate generic terminology.

Claim Objections

The Examiner objected to claims 73, 93, and 103, as these claims included misspelled words. Applicants corrected theses spelling errors and request that this objection be withdrawn.

Rejection under 35 USC § 112, Second Paragraph

The Examiner rejected claims 49-62, 64, and 73-110 under 35 USC § 112, Second Paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter, which Applicants regard as the invention. Applicants disagree with the Examiner and request thoughtful reconsideration of this rejection.

The rejection of Claims 62 and 110 is moot in view of cancellation of these claims.

The Examiner asserted that independent Claim 49, and dependent Claims 50-61, 64, and 73-110 were indefinite because Claim 49 is directed to a method for forming a cryopreserved tissue, but Claim 49 does not recite a cryopreservation step per se, but simply a "freezing" step. Applicants amended Claim 49 to clarify that Claim 49 is directed to preparing a tissue with reduced tissue damage, the method including the step of lowering the temperature of a solution and the tissue to at least the freezing point of the solution.

The Examiner asserted that Claim 53 was indefinite for reciting thawing tissue after it has been subjected to "extended storage." More specifically, the Examiner asserted that it is not clear how much time must elapse to be considered "extended storage." Applicants disagree and respectfully point out that claims are read in view of the specification. As defined by Applicants, for example at paragraph [0024] of the specification, "extended storage" means "at least three days, preferably, three days to ten years, and more preferably, one week to one year."

The Examiner asserted that Claim 58 is indefinite for being confusing in that it recites a temperature within "about +/-3°C." More specifically, according to the Examiner it is not clear what degree of deviation is tolerated by the claim. Applicants

amended Claim 58 to clarify that the thawed tissue has a denaturation temperature that may be reduced or increased by no more than 3° C from a denaturation temperature of the same type of native tissue.

According to the Examiner, Claim 73 is indefinite for being confusing in that it recites that "tissue" may be selected from a group comprising "blood cells" and "blood proteins." As amended, Claim 73 does not recite "blood cells" and "blood proteins."

According to the Examiner, Claim 80 is confusing in that it requires that the "tissue" be "decellularized." More specifically, the Examiner asserted that it is not clear how a substance can be considered tissue if it does not comprise cells. Applicants disagree with the Examiner's rejection of Claim 80. Applicants respectfully point out that Applicants do define decellularized tissue. Clams are read in view of the specification, wherein Applicants, for example at paragraph [0004], teach that tissue may be processed wherein the living, non-structural constituents within the tissue are reduced rendering the tissue decellularized. Accordingly, as defined by Claim 80, tissue may be decellularized tissue.

The Examiner asserted that Claim 82 is indefinite for reciting "isotonic" but not setting forth a point of comparison for the relative term. Applicants disagree with the Examiner's assertion. Applicants point out that, as used in Claim 82, the term "isotonic" referring to a buffer, is not a relative term and one of ordinary skill in the art would understand that an isotonic buffer, in context of Claim 82, means a buffer having the same concentration of solutes as any physiological fluid. Also, claims are read in view of the specification. As defined by Applicants in the specification, for example at paragraph [0037], "isotonic buffer system" is any buffer system that maintains a physiologically acceptable pH, from about pH 6 to about pH 8 (...) and that is compatible with the other solution constituents and the tissue (...)."

The Examiner asserted that Claim 93 is indefinite for reciting "long-chain polymers" without particularly pointing out either the character of the monomer units or the criteria for evaluating length. Applicants disagree with the Examiner and respectfully point out that a skilled artisan would understand that "long-chain polymers" consist of a chain of monomers of high relative molecular mass. For example, as

described in the specification at paragraph [0043], one non-limiting example of a long chain polymer, PVP has a molecular weight of about 17,000 (weight average). Also, "long-chain polymers" are known in the art as cell-impermeant substances. See, for example relevant pages of Bühler, Volker. Kollidon, Polyvinylpyrrolidone for the pharmaceutical industry. BASF Aktiengesellschaft, 1992, pp. 9, 122 (Appendix A).

The Examiner asserted that Claims 93 and 94 are indefinite for reciting a long list of constituents and "derivatives thereof" without limiting the manner in which a given compound might be related to the recited constituents or which related compounds are included or excluded by the claims. Applicants disagree with the Examiner. Applicants respectfully point out that Claims 93 and 94 are directed to a *method* of preparing a tissue with reduced tissue damage, including a cell-impermeant constituent selected from a group of specific compounds and their derivatives. As such, one of ordinary skill in the art would understand that Applicants are not claiming the compounds *per se*. Rather, the compounds listed in Claims 93 and 94 are included only as preferred examples of cell-impermeable constituents. Furthermore, because of the nature of the method claims, the only derivatives of a cell-impermeable constituents within the scope of these claims can be those capable of achieving the claimed method. Moreover, this term has been accepted by the U.S. Patent and Trademark Office and appears in method claims of patents in the area of sterilizing biological materials. See, for example, U.S. Patent No. 6,908,591B2 (cited in an IDS of August 15, 2005), claims 35, 37, and 38.

The Examiner asserted that Claims 93, 98, and 103 are indefinite for reciting both broad genera and narrow species within the genera, making it impossible to determine the scope of the claim. Applicants disagree with the Examiner. According to the MPEP 2173.05(h) "(...) The double inclusion of an element by members of a Markush group is not, in itself, sufficient basis for objection to or rejection of claims. (...) The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not necessarily render the scope of the claim unclear."

The Examiner also rejected Claim 103 as indefinite in that it recites "derivatives" and "analogs" of the recited constituents. Applicants disagree with the Examiner. Applicants respectfully point out that Claim 103 is directed to a *method* of preparing a tissue with reduced tissue damage, including a radical scavenger selected from a group of specific compounds, their derivatives, and analogs. One of ordinary skill in the art would understand that Applicants are not claiming the compounds per se. Rather, the compounds listed in Claim 103 are included only as preferred examples of radical scavengers. Furthermore, because of the nature of the method claim, the only derivatives or analogs of radical scavengers within the scope of Claim 103 can be those capable of achieving the claimed method.

Given the above, Applicants respectfully request that 35 U.S.C. § 112, First Paragraph rejection of Claims 49-61, 64, and 73-109 be withdrawn.

Rejection under 35 USC § 102(b)

Claims 49, 50, 52-65, 73, 81-90, 98, 101-106, 108, and 110 were rejected under 35 USC § 102(b) as being anticipated by US 5,328,821 to Fisher et al. (Fisher et al.).

The rejection of Claims 62 and 110 is moot in view of cancellation of these claims.

Applicants respectfully traverse this rejection because Fisher et al. does not disclose each and every element of Claim 49. As amended, Claim 49 comprises a step of irradiating the solution and the tissue. As admitted by the Examiner, the Fisher et al. reference does not teach irradiating the solution and the tissue. For this reason, Fisher et al. has clearly not taught Applicants' method that comprises the step of irradiating the solution and the tissue. Accordingly, this Section 102(b) rejection of Claim 49 and Claims 50, 52-61, 63-65, 73, 81-90, 98, 101-106, and 108 that depend on Claim 49, predicated on Fisher et al. should be withdrawn.

Rejection under 35 USC § 103

Claims 49, 50, 52-65, 73, 81-90, 98, 101-106, 108, and 110 were rejected under 35 USC § 103(a) as being unpatentable over US 5,328,821 to Fisher et al. (Fisher et al.) taken in view of US 4,798,611 to Freeman, Jr. (Freeman, Jr.). Also, Claims 49-65 and 73-110 were rejected under 35 USC § 103(a), as obvious over US 5,328,821 to Fisher et al. (Fisher et al.), taken in view of US 4,798,611 to Freeman, Jr. (Freeman, Jr.), and further in view of US 5,677,019 to Carstairs et al. (Carstairs et al.), US 6,140,123 to Demetriou et al. (Demetriou et al.), US 4,155,331 to Lawrence et al. (Lawrence et al.), US 5,279,964 to Christope (Christope), and US 5,403,834 to Malfroy-Camine et al. (Malfroy-Camine et al.). Applicants traverse the Examiner's rejection.

The rejection of Claims 62 and 110 is moot in view of cancellation of these claims.

The Examiner admits at page 10, line 11 of the Office Action that the Fisher et al. reference does not teach irradiating the solution and the tissue. The Examiner asserts that Freeman, Jr. teaches that the gamma irradiation efficiently sterilizes tissue and tissue matrices and that the irradiation does not degrade the tissue so treated. The Examiner further asserts that it would have been obvious to use the irradiation step of Freeman, Jr. on the cryopreserved tissue of Fisher et al.

The rejection of the claims under 35 USC § 103(a) is respectfully traversed. Applicants point out that the Examiner has not established a *prima facie* case of obviousness under 35 U.S.C. § 103 as a basis for rejection of these claims.

At the outset, the Examiner has not provided evidence in Fisher et al. or in the prior art as a whole of a valid suggestion or motivation to combine and/or modify the disclosures of Fisher et al. and Freeman, Jr. to provide the method of the Applicants' claims. The only suggestion or motivation provided in the Office Action are conclusory statements without support therefor that one of skill in the art "would have been motivated to use the irradiation step of Freeman, Jr. on the cryopreserved tissue of Fisher et al. for the expected benefit of preventing microbial infestation of the tissue, allowing it to be used later for transplantation procedures." This statement is not a suggestion or motivation to combine Fisher et al., performing crypreservation of tissue

in an *aqueous* preservation solution, with Freeman, Jr., performing sterilization by irradiating *glutaraldehyde*-treated, and thus cross-linked, tissue. There is not even a suggestion in Fisher et al. that further treatment of any kind, let alone irradiation, would be desired for tissue preserved in the aqueous solution of Fisher et al. As noted in MPEP 2143.01, with reference to *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990):

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless **the prior art suggests** the desirability of the combination. [emphasis added]

Without a suggestion or motivation to combine these two references, the Examiner's § 103 rejection is inappropriate and should be withdrawn.

Moreover, because the method described by Freeman, Jr. is directed at sterilizing cross-linked tissue, the method, in fact, teaches away from Applicants' invention by requiring treating the tissue with a cross-linking solution, including glutaraldehyde, prior to the irradiation step. In contrast, the method of Applicant's invention requires that the tissue be combined with a solution in a method that reduces tissue damage when, for example, (1) the temperature of the tissue and the solution is lowered, and (2) the tissue and the solution are irradiated. Consequently, a combination of the Fisher et al. and Freeman, Jr. references would result in tissue that has been glutaraldehyde cross-linked and cryopreserved. As such, this combination, even if proper, would not have made Applicants' invention obvious.

Furthermore, as admitted by the Examiner, neither Fisher et al. nor Freeman, Jr. addresses each and every embodiment for components of the solution used in the method of dependent claims 50-65 and 73-110 (See Office Action, page 12, lines 15-17). However, the Examiner, with the benefit of hindsight, asserts that it would have been obvious to combine the teaching of Fisher et al. and Freeman, Jr. with the other five references. Applicants assert that the diversity of the other references indicates that such a combination would not have been obvious at the time of filing. Note the wide variety of subjects covered in these references:

- Carstairs et al. disclose methods of preserving *plant* tissue with a solution that includes dihydric alcohols.
- Dimetriou et al. teach cryopreserving cells with a specific cryopreservation medium.
- Lawrence et al. teach a method of cryopreservation of multicellular organisms, such as *immature marine crustaceans* by exposing the organisms to a cryopreservation medium.
- Christope teaches an *inoculation device*, including a handle together with microorganisms, for transferring and storing for extending periods.
- Malfroy-Camine et al. teaches *antioxidant complexes* for treatment and prevention of tissue damage by free radicals.

The diversity of these references indicates that the Examiner's combination for this § 103 rejection is improper.

Moreover, even if properly combined, these references still fail to teach each and every element of Applicants' invention. Applicants submit that Claims 49-65 and 73-110 include limitations that are not found in Carstairs et al, Dimetriou et al., Lawrence et al., Christope, or Malfroy-Camine et al. For example, none of these references teach or suggest that the solution is degassed (Claim 49), that the tissue and the solution are placed in a package before freezing (Claim 50), that the tissue is sterilized after the packaging step (Claim 60), etc. Also, with regards to the different components of the solution as defined, for example, in Claims 83-85, 90, 93-95, 98-100, and 103-105, although a few of the exemplary components of Applicants' solution are recited in the cited references, Applicants respectfully point out that Applicants are not claiming these components *per se*. Rather, Applicants claims are directed to a method for preparing a tissue with reduced tissue damage and the components listed, for example, in Claims 83-85, 93-95, 98-100, and 103-105 are included only as preferred examples of components of a solution that is used in that method, as defined by Claim 49.

For at least these reasons, the Examiner's § 103 rejections should be withdrawn.

CONCLUSION

Applicants respectfully submit that the present application is now in condition for allowance. Should the Examiner feel a discussion would expedite the prosecution of this application, the Examiner is kindly invited to contact the undersigned at (312) 245-5398.

Respectfully submitted,

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Magdalena O. Cilella, Ph.D.
Reg. No. 56,619
Agent for Applicant
Customer No. – 00757 Brinks Hofer Gilson & Lione

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, IL 60610
(312)321-4200

APPENDIX A

Volker Bühler

Kollidon®

Polyvinylpyrrolidone for the pharmaceutical industry

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BASF Aktiengesellschaft
Feinchemie
D-6700 Ludwigshafen

BASF

August 1992

1 General notes on synthesis and applications

1.1 Soluble polyvinylpyrrolidone (soluble Kollidon grades)

Modern acetylene chemistry is based on the work of Reppe at BASF. One of the many products of this work is N-vinylpyrrolidone (Fig. 1).

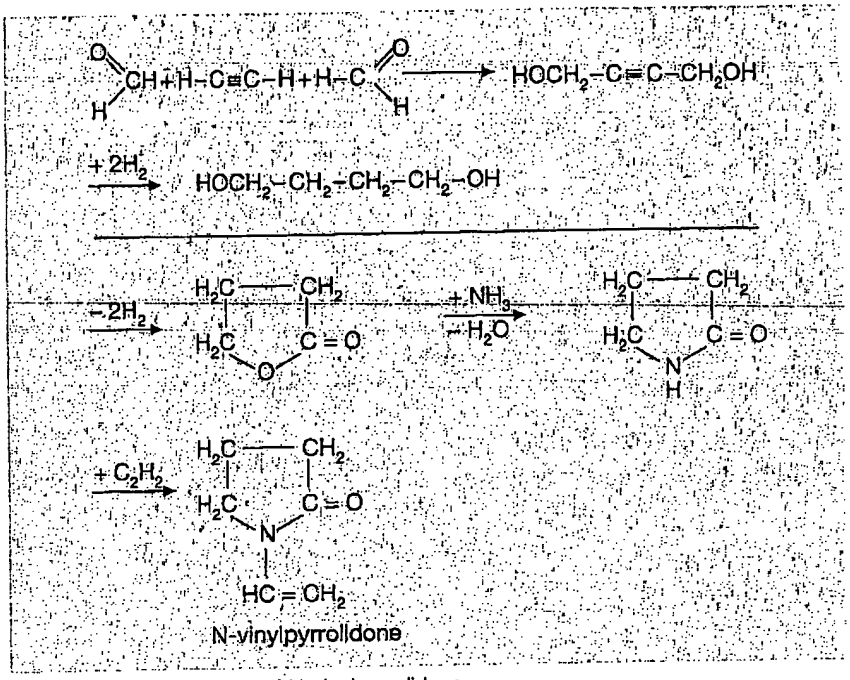

Fig. 1: Reppe's synthesis of N-vinylpyrrolidone

The first polymerization product of N-vinylpyrrolidone was soluble polyvinylpyrrolidone, which was patented in 1939. Fig. 2 shows one of the mechanisms of polymerization: free-radical polymerization in water using hydrogen peroxide as initiator [1, 141].

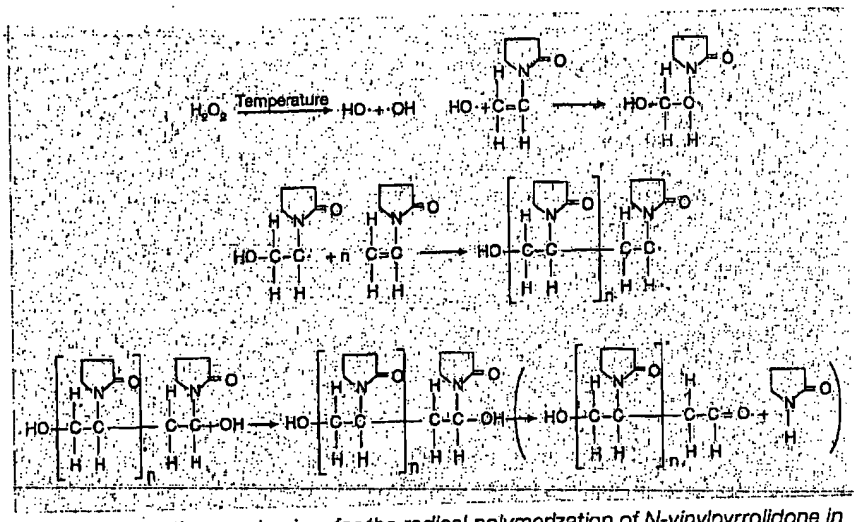

Fig. 2: The reaction mechanism for the radical polymerization of N-vinylpyrrolidone in water

The mechanism for terminating the polymerization reaction makes it possible to produce soluble polyvinylpyrrolidone of almost any molecular weight.

Apart from the method of production in water shown in Fig. 2, it is also possible to conduct the polymerization in an organic solvent, e.g. isopropanol. This technology is used today in the production of low-molecular polyvinylpyrrolidone for injection solutions.

The low and medium-molecular weight grades of soluble polyvinylpyrrolidone are spray-dried to produce the pharmaceutical-grade Kollidon powders, while the high-molecular weight grades are roller-dried.

Soluble polyvinylpyrrolidone was first used during World War II as a blood-plasma substitute. Although it has excellent properties for this purpose, it has no longer been used for a number of decades. The organism does not metabolize the polymer, with the result that after parenteral administration, small quantities of high-molecular components may remain within the body. This problem does not exist with oral administration.

Today, soluble polyvinylpyrrolidone (e.g. Kollidon) is one of the most versatile and widely used pharmaceutical auxiliaries (see Chapter 2.4 "Soluble Kollidon grades").

It is also used in the production of one of the most important topical disinfectants, PVP-Iodine.

1.2 Insolub

Insoluble po
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Fig. 3: Produ

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With the methods given in Table 90, great care must be taken that no high-molecular povidone can be leached out of or peeled away from the plastics material. Kollidon 90 and Kollidon 30 become insoluble hydrophilic substances after crosslinking. Alkaline treatment, e.g. with sodium hydroxide is a well-established and effective method [1, 141, 217]. Crosslinking by irradiation is also described in the literature [371].

2.4.8.4 Reduction of the toxicity of active ingredients and other substances

Because of their ability to form complexes with a large number of substances (see Sections 2.2.7, 2.4.3 and 2.4.5) Kollidon can be used to reduce the toxicity of certain active substances (Table 91). This effect is mainly used with active substances such as oxytetracycline, that are given parenterally as well as those that are applied topically to the skin and to the eye (e.g. iodine, oxymetazoline).

Table 91: Examples of pharmaceutical active substances whose reduction in toxicity by complexation with soluble Kollidon is described in the literature

Active substance	Administration				Literature
	Parenteral	Topical	Ocular	Oral	
Azapropazone	–	–	–	+	[284, 319]
Floctafenine	–	–	–	+	[284, 319]
Glafenine	–	–	–	+	[284, 319]
Indomethacin	–	–	–	+	[123]
Iodine	–	+	(+)	–	[124]
Mefenamic acid	–	–	–	+	[284, 319]
Oxymetazoline	–	–	+	–	
Oxytetracycline	+	–	–	–	[22, 373, 374]
Polymyxin B	+	–	–	+	[489]

Not only can the toxicity of active substances be reduced by Kollidon. The irritant or toxic effects of other substances such as cyanides, nicotine, formaldehyde, formamide, and other toxins, with which povidone forms complexes of adequate stability, can also be reduced [126].

2.4.8.5 Cryopreservation

The inhibition of the crystallization of water and active substances by povidone has been investigated in a number of publications with respect to the freeze-drying of histological specimens. This cryoprotective effect of the soluble Kollidon grades therefore plays a greater role in biotechnology than in the manufacture of pharmaceuticals (see also Section 2.4.5.3).

2.4.8.6 Stabilization of enzymes

The soluble Kollidon grades, particularly Kollidon 30, can be used to stabilize many enzymes, as is extensively described in the literature. Complexation also plays a role here in binding deactivating substances such as

phenols and ta
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the literature, c
povidone.

Table 92: The st

Asparaginase
beta-Interferon
Catalase
Dehydrogenas
Ferrochelatase
Galactosidase
Glucose oxida
Hyaluronidase
Peroxidase
Phenolase
Prostaglandin
Pyruvate carbo
Transaminase
Urease

2.4.8.7 Stabil

The soluble Kc
active ingredie
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formulation for
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without the ad
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Table 93: Vitam

1. Formulation
Thiamine h
Riboflavine
Nicotinami
Pyridoxine
Cyanocob
EDTA sodi
Propyl gall
Kollidon 17